REMARKS

Claims 21-42 are pending. After consideration of the Appeal Brief filed April 14, 2010, prosecution of the present application was reopened and the pending Action issued.

The present invention is directed to pharmaceutical compositions that achieve improved oral bioavailability of basic drug compounds over those compositions of the prior art. Specification at page 3, lines 1-15. These compositions are semi-solids or solids (*id.* at page 108, lines 1-13) and comprise the basic drug compound (*id.* at page 4, lines 31-33), Vitamin E TPGS (*id.* at page 9, lines 5-6), and a physiologically tolerable water-soluble acid (*id.* at page 9, lines 14-19). The ratio of the acid:drug compound ranges from 1:1 to 100:1, by weight (*id.* at page 9, line 36-38).

Rejection under 35 U.S.C. § 102

Claims 21-29, 31, 32, and 34-42 stand rejected under 35 U.S.C. § 102 (a)/(e) as allegedly anticipated by U.S. 6,919,370 (Chen1) in view of U.S. Published Application No. 2008/0160106 (Fais) and Casodex. The Applicants disagree and request withdrawal of the rejection.

"Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim. The requirement that the prior art elements themselves be 'arranged as in the claim' means that the claims cannot be 'treated as mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that give the claims their meaning. Unless a reference discloses . . . not only all of the limitations claimed but also all of the limitations ***arranged or combined in the same way as recited in the claim***, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, (Fed. Cir. 2010) (emphasis added).

Chen1 does not anticipate the claimed invention because there is no disclosure of every limitation of the claims "arranged or combined in the same way as recited in the claim" as the law dictates. The rejection merely compiles various, unrelated sections of Chen1, alleging how

each section might read on a different limitation of the claims. This is legally insufficient. It cannot be disputed that Chen1 fails to provide a sufficient disclosure of an embodiment in which all claim elements are as arranged in the claims. Every example described by Chen1 is a liquid formulation, which the Examiner has admitted is clearly outside the scope of the solids and semi-solids of the claims. *See* December 17, 2009 Action at 3 ("Whereas the claimed invention requires the pharmaceutical composition to be a semi-solid or solid, Chen Formulation 1-13 are directed to liquid concentrate formulations."). Moreover, while the Examiner uses Fais and Casodex to establish that cisplatin and bicalutamide are basic drug compounds that allegedly fulfill a limitation of the claims, at page 17 of the pending Action, the Examiner concedes that "Chen1 does not teach an example having cisplatin or bicalutamide as the cancer drug." For at least these reasons, Chen1 cannot anticipate the present claims.

The Examiner is treating the claims as a "catalog of separate parts," rather than identifying where, in a single reference, the invention is described ***as claimed***. The rejection is improper and should be withdrawn.

Rejection under 35 U.S.C. § 103

Applicants note that the first rejection cited under the heading "Claim Rejections – 35 U.S.C. § 103" states that the rejection is an anticipation rejection under 35 U.S.C. § 102(a,e). As later comments in the rejection refer to factors pertaining to obviousness, Applicants assume this is a typographical error and will respond to the rejection as a rejection under 35 U.S.C. § 103.

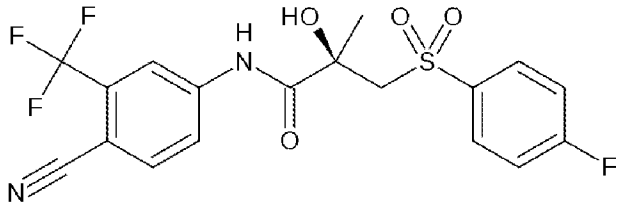
Claims 21-29, 31, 32, and 34-42 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Chen1 in view of Fais and Casodex. Fais is used to support the allegation that cisplatin is a weak basic drug. Casodex is used to support the allegation that bicalutamide is a basic drug with a pKa of 12.

In order to support a prima facie case of obviousness, the Office must establish some motivation or suggestion, either in the references or in the skill of the art, to modify the reference to arrive at the claimed invention. Furthermore, the Supreme Court has dictated that the Office must also establish that the modification would have resulted in predictable results with a

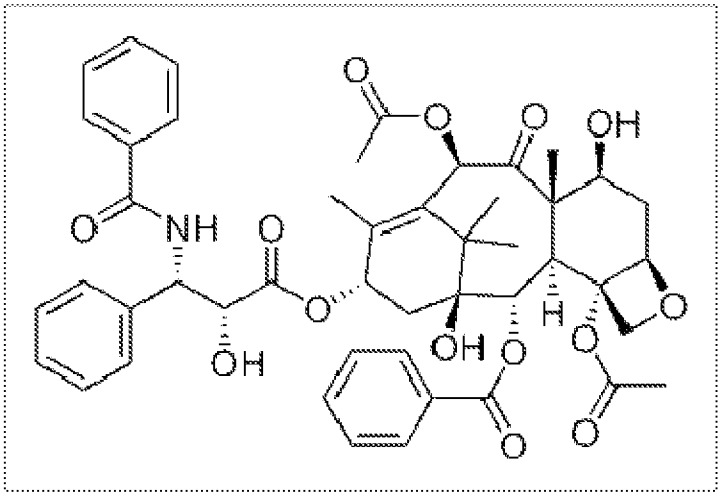
reasonable expectation of success. The Office has failed to meet its burden and Applicants request withdrawal of the rejection.

Chen1 is directed solely to formulations of paclitaxel, which is not a basic drug compound as required by the present claims. Despite the Examiner's attempts to point to various "laundry lists" of drug compounds, acids, polymers, bulking agents, etc., those of skill in the art know that paclitaxel can only be administered intraveneously. Chen1 at col. 2, lines 27-47. Indeed, every formulation exemplified in Chen1 is to a liquid concentrate of paclitaxel. Chen1 is devoid of any examples of solid or semi-solid formulations. Citation to passing references of oral administration, tablets, or suspensions is disingenuous as no such formulations of paclitaxel are described in the reference or are known in the art. As such, no one skilled in the art would have been motivated to modify the intravenous liquid formulations of Chen1 to arrive at the claimed solids and semi-solids.

In addition, the Examiner alleges that one skilled in the art would have substituted cisplatin or bicalutamide for the paclitaxel in the formulations described in Chen1 because he "would have expected success because Chen1 suggested using other cancer drugs, such as cisplatin or bicalutamide." No such suggestion is made in Chen1. One skilled in the art would not have reasonably expected that substituting chemically unrelated compounds such as the platinum-based cisplatin ($Cl_2Pt(NH_3)_2$) or bicalutamide:



for paclitaxel:



used in Chen1 would predictably lead to a successful formulation. In fact, Chen1 describes the difficulties associated with formulation chemistry:

> It is well documented that physical and chemical properties, such as stability, solubility, dissolution, permeability, and partitioning of most pharmaceuticals are directly related to the medium in which they are administered. And, in turn, the physical and chemical properties of drug-in-formulation mixtures affect the pharmacological and pharmacokinetic properties, such as absorption, bioavailability, metabolic profile, toxicity, and potency. Such effects are caused by interactions between the formulation's components and the pharmaceutical and/or interactions between the components themselves. . . . Thus, discovery of pharmaceutical formulations that optimize bioavailability and duration of action of the pharmaceutical and minimize undesirable properties is an important part of pharmaceutical development and research.

Chen1 at col. 1, lines 27-45.

Clearly, one skilled in the art would not have reasonably expected that a formulation designed specifically for paclitaxel could also be used successfully for cisplatin or bicalutamide. For at least these reasons, the rejection is improper and should be withdrawn.

Claims 21-42 stand rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. 6,828,301 (Chen2) in view of WO 01/22938 (Verreck). The Applicants disagree and request withdrawal of the rejection.

Chen2 teaches that improved dispersion and dissolution performance can be achieved by adding a surfactant to a pharmaceutical composition that comprises a drug compound and an amine. Chen2 at col. 15, lines 45-60, col. 15, line 61-col. 16, line 28. Vitamin E TPGS is identified in Chen2 as a compound that has surfactant properties. *Id.* at col. 15, lines 45-60. Importantly, however, Chen2 attributes the improved bioavailability described therein, not to the surfactant, but to the amine in the formulation. "It has been found that incorporation of a basic amine in a solid dosage form improves the in vitro dissolution rate significantly." Chen2 at col. 41, lines 33-35.

Verreck describes basic drug compounds suitable for use as antivirals. Verreck indicates that these compounds can be melt extruded with one or more water-soluble polymers, for example hydroxypropyl methylcellulose (HPMC), to form particles. Verreck at page 1, lines 5-9; Example 4. These solid dispersions are said to be able to improve the bioavailability of the drug compound. Verreck at page 1, lines 11-13. Verreck suggests that addition salts can be made from the compounds described therein by combining the compound with an inorganic or organic acid. Verreck at page 10, lines 1-9. Verreck does not describe the use of Vitamin E TPGS.

The Examiner has failed to meet its burden in establishing a *prima facie* case of obviousness, *i.e.*, he has failed to demonstrate the requisite motivation to combine Chen2 with Verreck in order to arrive at the claimed invention. Chen2, while describing surfactants generally, identifies that improved oral bioavailability is achieved ***with basic amines***, not with Vitamin E TPGS and a physiologically tolerable water-soluble acid. Verreck fails to describe the use of any surfactants. Indeed, Verreck relies on water-soluble polymers to form particles having improved bioavailability.

In cases where researchers "can only 'vary all parameters or try each of numerous possible choices until one possibly arrives at a successful result, where the prior art gives either no indication of which parameters are critical or no direction as to which of many possible

choices is likely to be successful,'" the Examiner "should not succumb to hindsight claims of obviousness." *P&G v. Teva Pharms. USA, Inc.,* 566 F.3d 989, 996-97 (Fed. Cir. 2009). "Patents are not barred just because it was obvious to explore [a general approach] that seemed to be a promising field of experimentation where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* There is no suggestion or motivation in the cited art that would have led the skilled person to incorporate any surfactant, let alone the specific Vitamin E TPGS presently claimed, into the compositions described in Verreck. As the Examiner has failed to identify the any motivation to combine the cited references to arrive at the claimed invention, he has failed to establish the *prima facie* obviousness of the claimed subject matter. Accordingly, the rejection is improper and should be withdrawn.

The Unexpected Oral Bioavailability of the Compositions of the Invention Would Have Been Surprising and Unexpected to a Person of Ordinary Skill in the Art

Even if the claimed invention is obviousness over the cited art, and Appellants do not concede this point, obviousness may be rebutted based on "unexpected results" by demonstrating that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *P&G*, 566 F.3d at 994. Here, a showing of unexpected results sufficient to rebut a showing of obviousness has been presented to the Examiner during prosecution of the application, yet the Examiner has not addressed the patentability of the claimed invention in view of those results.

As described in the Declaration of Marcus Brewster that was submitted on September 16, 2009, Vitamin E TPGS gave surprisingly higher average supersaturation as compared to Cremophor RH40 and Polysorbate 20 with this effect being seen over a range of compounds having varying physicochemical properties. Declaration of Marcus Brewster at ¶ 4. Vitamin E TPGS also provided better stability of the formed supersaturated solution than either Cremophor RH40 or Polysorbate 20. *Id.* at ¶ 5. Significantly, an oral bioavailability of ***100%*** was achieved with a composition of the invention, compared to only 30% and 60% achieved with PEG400 and Cremophor RH40, respectively, *Id.* at ¶ 7. This surprising result is also unexpected. *Id.* at ¶ 9.

Nowhere in the present Action is the Declaration addressed. In a prior Action, the Examiner summarily dismissed the data submitted for his consideration. The Examiner dismissed the Appellants' evidence, stating simply that it was "unpersuasive because Chen 301 teaches the prefer[red] surfactant is TPGS." Action at 4. Chen 301 notes that "Preferred surfactants include Vitamin E TPGS, Pluronic F68, or sodium lauryl sulfate, and mixtures thereof." col. 15, lines 56-58. Simply because a surfactant is identified as "preferred" does not provide any indication to the skilled person that the surfactant would demonstrate the unexpected supersaturation, stability, and oral bioavailability properties presently observed with Vitamin E TPGS, as used in the present invention. The Examiner summarily dismissed the presented evidence without setting forth sufficient facts and reasoning to justify his conclusion and improperly accorded the submitted evidence no weight, even though the evidence clearly "establish[ed] a nexus between the rebuttal evidence and the claimed invention." MPEP 2145. As the evidence of record clearly demonstrates the unexpected and surprising results achieved with the claimed invention, withdrawal of the rejection is requested.

Obviousness type double patenting

Several obviousness type double patenting rejections have been raised. Applicants note that U.S. App. Nos. 11/733,507 and 11/204,513 are abandoned. The rejections over these applications are deemed moot and will not be addressed. As to the remaining rejections, the present claims are patentably distinct over the cited art and the patenting of the present claims does not unjustifiably extend the patent term of any of the cited patents.

Each of the rejections in view of U.S. 7,241,458; U.S. 7,037,917; U.S. 6,878,717; and U.S. App. No. 11/930,835 is based on the disclosure of Chen2, which has been addressed above. For at least the reasons stated above, the disclosure of Chen2 does not support the allegations asserted by the Examiner and is insufficient to establish that the present claims are not patentably distinct over each of the cited art. Moreover, the Declaration of Marcus Brewster clearly establishes the unexpected results, and thus patentability of the claims. Withdrawal of the rejections is requested.

Claims 21-42 are patentable over the cited art. Withdrawal of the rejections and allowance of the claims is requested.

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